AWARD NUMBER: W81XWH-15-1-0576

TITLE: Biofidelic Three-Dimensional Brain Surrogate Models of mTBI-Induced Alzheimer's Disease Pathology

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REPORT DATE: October 2016

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE		*Form Approved OMB No. 0704-0188*
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. **PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.**		
1. REPORT DATE October 2016	**2. REPORT TYPE** Annual	**3. DATES COVERED** 15 Sep 2015 - 14 Sep 2016
4. TITLE AND SUBTITLE Biofidelic 3-Dimensional Brain Surrogate Models Of mTBI Induced Alzheimers Disease Pathology		**5a. CONTRACT NUMBER** **5b. GRANT NUMBER** W81XWH-15-1-0576 **5c. PROGRAM ELEMENT NUMBER**
6. AUTHOR(S) 1. Utkan Demirci, PhD (PI) 2. Zezong Gu, MD, PhD (Co-PI) E-Mail: utkan@stanford.edu; guze@health.missouri.edu		**5d. PROJECT NUMBER** **5e. TASK NUMBER** **5f. WORK UNIT NUMBER**
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) 1. Leland Stanford Juniior University 3155 Porter Drive, Stanford, CA 94305 2. University of Missouri, 1 Hospital Drive, Columbia, MO 65212		**8. PERFORMING ORGANIZATION REPORT NUMBER**
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012		**10. SPONSOR/MONITOR'S ACRONYM(S)** USAMRMC **11. SPONSOR/MONITOR' NUMBER(S)**
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited		

13. SUPPLEMENTARY NOTES
None

14. ABSTRACT

The vast complexity of the brain, with its hundred billion neurons and supporting cells and hundreds of trillion connections poses a tremendous roadblock for scientists to understand the workings of the brain on the molecular, cellular or circuit levels. Defining the genetic programs that drive neural function, the cell-type specific contributions to neural circuit workings, the mapping of connectivity patterns within and between individual networks, and elucidating the mechanisms of disease present only a few examples of the challenges. Novel approaches and technologies are needed that complement and advance the state-of-the art in vivo, ex vivo, and in vitro approaches to study brain physiology and diseases. Here, we are proposing to bioengineering a validated *in vitro* 3-dimensional (3D) brain surrogate mTBI/AD model built of primary neurons. Our research proposal builds upon the shock wave model of mTBI, which postulates that mTBI is caused by the primary shock wave from a blast that penetrates through the skull and traverses the brain. We will use this to elucidate the mechanisms leading to open field blast explosives induced mTBI and its relationship to Alzheimer's disease, including discovery by proteomic, genomic, and *in vivo* analysis of mice of new mTBI/AD biomarkers and disease pathways.

15. SUBJECT TERMS
Engineering a validated *in vitro* 3-dimensional (3D) brain surrogate mTBI/AD model

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON** USAMRMC
a. REPORT Unclassified	**b. ABSTRACT** Unclassified	**c. THIS PAGE** Unclassified	Unclassified	25	**19b. TELEPHONE NUMBER** *(include area code)*

Standard Form 298 (Rev. 8-98) Prescribed by ANSI Std. Z39.18

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1. INTRODUCTION:

Three-dimensional (3D) surrogate models that mimic the actual geometry, composition, and function of neural circuits present the most physiologically relevant in vitro system to study brain physiology in health and disease. However, contrary to other research fields (e.g., immunology, cancer), neuroscience still lacks an in vitro setting to examine cellular function in 3D in densely wired, heterogeneous tissues. Novel approaches and technologies are needed that complement and advance the state-of-the art in vivo, ex vivo, and in vitro approaches to study brain physiology and diseases. Here, we are proposing to bioengineering a validated *in vitro* 3-dimensional (3D) brain surrogate mTBI/AD model built of primary neurons. Our research proposal builds upon the shock wave model of mTBI, which postulates that mTBI is caused by the primary shock wave from a blast that penetrates through the skull and traverses the brain. We will use this to elucidate the mechanisms leading to open field blast explosives induced mTBI and its relationship to Alzheimer's disease, including discovery by proteomic, genomic, and *in vivo* analysis of mice of new mTBI/AD biomarkers and disease pathways.

2. KEYWORDS:

3-D Brain Models, Alzheimer's Disease, Traumatic Brian Injury, Neural Tissues

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The objective of our research is to bioengineer a validated *in vitro* 3-dimensional (3D) brain surrogate mTBI/AD model built of primary neurons. Our research proposal builds upon the shock wave model of mTBI, which postulates that mTBI is caused by the primary shock wave from a blast that penetrates through the skull and traverses the brain. The resulting ultrastructural damage and injuries to nerve cells at molecular, cellular and brain circuit level may lead to mTBI/AD pathology. We will use this to elucidate the mechanisms leading to open field blast explosives induced mTBI and its relationship to Alzheimer's disease, including discovery by proteomic, genomic and *in vivo* analysis of mice of new mTBI/AD biomarkers and disease pathways.

What was accomplished under these goals?

As specified in **Subtask 9 (Aim3)**, our team at the University of Missouri (UM) has worked on the logistic aspects proposed for the development of our experimental systems for modeling of combat blasts using military relevant open field explosive damage paradigms.

Major activities

1. Animal protocols for the work at the University of Missouri (UM) are approved by DoD.
2. Dr. Gu and his UM team have communicated with explosives engineers regarding the open field blast sites for biological studies, and made several site visits checking the blast settings for the experiments and animal acclimating unit on the site.
3. The Dr. Gu team in Columbia and Dr. Johnson's team in Rolla have tested the newly purchased pencil gauge probes and the cables for the blast pressure measurement and the animal holding platform.

4. The animal acclimating unit has been installed on the place and is running well. This place is closed to the open field blast site within the Explosives Research Facility in Rolla, but shielding the animals from explosives on the open field blast site. The ventilation unit with temperature control and electricity with 12-hr timed lights in accordance with animal welfare (see ACURO appendix) has been installed.
5. Animals were tested on the effects of transportation between Columbia and Rolla and housing in the animal acclimating unit on the blast site for 5 days. No significant changes on behaviors (eating and drinking) were observed.
6. The UM team along with Director of the University Animal Care Quality Assurance (Dr. Henegar, Jeffrey R) and Director of Office of Animal Resources & Clinical Associate Professor, Office of Animal Resources (Dr. Dixon, Lonny W) had visited open field blast sites for the animal housing and care issues.
7. UM engineers in Rolla designed and built animal holding racks on the platform for the blast experiments on the open field based on the publications from other groups.
8. The UM team tested the open field explosive settings in order to induce mTBI/AD in vitro and in vivo. The setting includes monitoring devices such as ultra-speed camera and pressure gauges and connection cables.
9. Mouse brain tissues have been prepared for the study on electronic microscope with three groups: sham, 7 days or 30 days after blast. Working on the EM will help us to understand the ultrastructure changes due to blast.
10. Example of EM images (Figure 1):

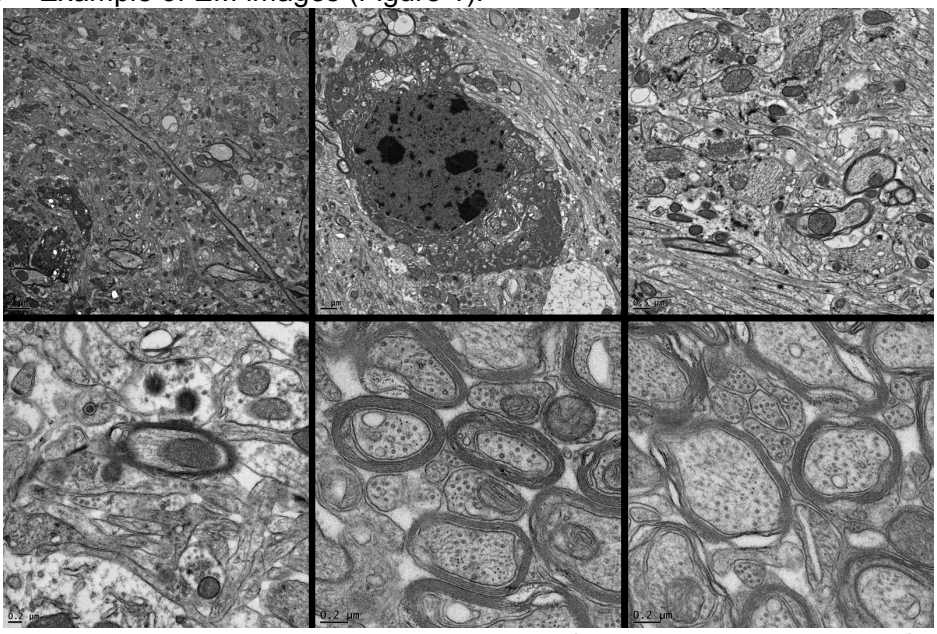

Figure 1: Ultrastructural examination of the cortical region of mouse brain. Representative microphotograms of transmission electron microscopy (TEM) of the sham-control mouse brain indicates high quality for TEM tissue preparation and imaging at the University of Missouri EM Core Facility in order to examine open field blast-induced mild traumatic brain injury for ultrastructural features of neurons and glial cells, cytoplasmic organelles, as well as myelin sheaths and axon bundles. Normal myelinated axons appear with a tightly wrapped sheath located near the axon. Scale Bar, 2, 1, 0.5 μm (upper left, middle and right panels, respectively); and 0.2 μm (lower panels).

11. Dr. Demirci's team has performed experiments to demonstrate the ability to grow primary neurons isolated from mouse in 3D *in vitro* cultures using different biomaterials such as Matrigel and GelMA (methacrylated gelatin) hydrogels. The viability assay results demonstrated that utilizing GelMA is better for long-term 3-D culture of primary neurons compared to Matrigel (Figure 2).

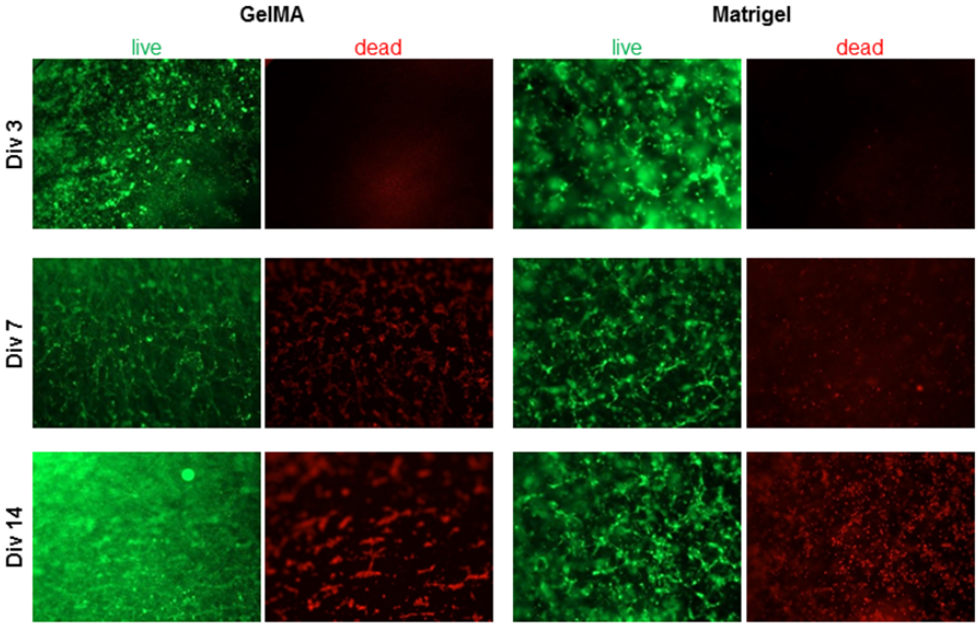

Figure 2: Comparison of viability of neurons grown in GelMA and Matrigel hydrogels. Mature neurons grown in GelMA shown higher cell viability compared to Matrigel.

12. Dr. Demirci's team has also demonstrated that cortical neurons grown in GelMA formed a 3-D network with synaptic connections. These 3-D in vitro cultures are ready to be shipped for testing in the blast experiments.

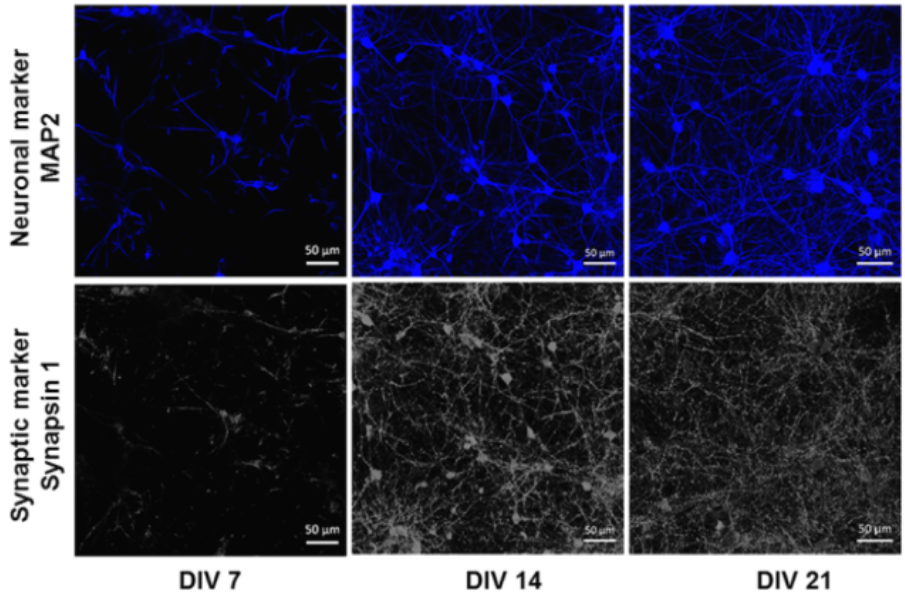

Figure 3: 3D network of neurons with synaptic connections in GelMA hydrogel.

What opportunities for training and professional development has the project provided?

In parallel with the specific aims of this project, at Stanford, we trained and mentored several students such as: a) students from High Schools and; b) undergraduate student from University of California at San Diego, Santa Barbra, Davis, and Berkeley; c) visiting graduate student from Germany, Portugal and China. Students were trained with cell culture, neuron isolation, histological analysis techniques.

How were the results disseminated to communities of interest?

Results were disseminated through the following talks:

National

2016: What is Innovation?/ Research Presentation, Engineering Deans Institute (EDI) at the American Society for Engineering Education Meeting, San Francisco, CA (invited panel talk)

2016: Label-free Magnetic Additive Biomanufacturing Methods to Isolate, Sort Circulating Tumor Cells, and Microemboli/ Research Presentation, College of Engineering & Computer Science, Florida Atlantic University (invited talk)

2016: Micro- and Nano-scale Technologies for Applications Medicine/ Research Presentation, AES Electrophoresis Society's Annual Meeting, San Francisco, CA (plenary talk)

2016: Label-free Magnetic Levitation Technologies for Monitoring Health and Disease /Research Presentation, Point of Care Diagnostics: Design, Development, and Adoption Virtual Symposium, BioPharma Research Council, Tinton Falls, NJ (keynote speaker)

International

2016: Micro- and Nano-scale Technologies for Applications Medicine//Research Presentation, University of Alberta, Alberta, Canada (Invited Talk)

2016: Magnetic Levitation and Faraday patterns in 3D Bioprinting/Research Presentation, New Directions in Bioprinting-International Conference, Skolkova Institute of Science and Technology, Moscow, Russia (Invited Talk)

2016: Microscale Technologies for Bioengineering Applications in Medicine/Research Presentation, Dr. John W. McGregor Memorial Lecture, University of Alberta, Canada (Invited Keynote Speaker)

2016: Assembly and Joining Needs in Bio-N/MEMS/ Research Presentation, International Conference on Nanojoining and Microjoining, Niagara Falls, Ontario, Canada, 2016 (Invited Keynote Speaker)

What do you plan to do during the next reporting period to accomplish the goals?

We aim to create in vitro 3D neuronal and astrocyte tissue models towards to Aim 1, SubTask2 Bioengineering approach to create 3D neuronal and astrocyte models, using photolitograhpy methods.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

This bioengineering approach presented several crucial advances and benefits for studying mTBI/AD. Here, we first provide 3D model systems for developing the most naturalistic approximation of the brain *in vitro,* thus elucidating the etiology of human brain disorders. We also examine the chemical composition of hydrogels for dense encapsulation of neurons in 3D geometries for generating a more appropriate microenvironment than the aqueous nature of conventional 2D cultures. We provide specific cell manipulation techniques in 3D systems, which are the same ease of manipulation as traditional 2D neuronal cultures in neuroscience research, as well as minimize challenges *in vivo* systems, including cost, limitation in analysis, throughput and freedom of manipulation, risk of inconsistent readout due to animal variability and need of skilled technical personnel. By combining these multiple aspects, we demonstrate an excellent mimicry model to study the impact of brain trauma in general, and in particular of shock waves that cause ultrastructural damage and loss of brain functionality of as it relates to mTBI/Alzheimer's disease pathology.

What was the impact on other disciplines?

In addition to the neurobiology, the presented bioengineering approach has broad impact on multiple disciplines, including genetics, molecular biology, biomaterials, biophysics, chemistry, biomimetics, and bioinspired technologies.

What was the impact on technology transfer?
Nothing to Report

What was the impact on society beyond science and technology?

This bioengineering approach has great impact over civil and army personnel having mild traumatic brain injury or Alzheimer's disease (AD) associated pathology. This approach will open new avenues to understand the mechanism(s) that cause blast induced mTBI/AD pathology, and it will especially help the diagnosis, monitoring, prevention and treatment of brain damage in soldiers. Compared to existing *in vivo* and *ex vivo* systems, biofidelic 3D systems are easy-to-use, cost-effective, and allow multiple parallel testing of many experimental conditions. From a broad perspective, this approach provides a versatile platform that is potentially adapted to other neurologic disorders (e.g., Parkinson's disease), infection diseases, and non-communicable diseases such as diabetes and cancer.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change
Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them
Nothing to report.

Changes that had a significant impact on expenditures
Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report.

Significant changes in use or care of human subjects
Nothing to report.

Significant changes in use or care of vertebrate animals.
Nothing to report.

Significant changes in use of biohazards and/or select agents
Nothing to report.

6. PRODUCTS:

Publications. Song H, Cui J, Simonyi A, Johnson CE, Hubler GK, DePalma RG, Gu Z. Linking blast physics to biological outcomes in mild traumatic brain injury: Narrative review and preliminary report of an open-field blast model. Behav Brain Res. 2016 Aug 21. pii: S0166-4328(16)30555-1. doi: 10.1016/j.bbr.2016.08.037. [Epub ahead of print] PubMed PMID: 27555538.

Journal publications.
Nothing to report.

Books or other non-periodical, one-time publications
Nothing to report.

Other publications, conference papers, and presentations.

National

2016: What is Innovation?/ Research Presentation, Engineering Deans Institute (EDI) at the American Society for Engineering Education Meeting, San Francisco, CA (invited panel talk)

2016: Label-free Magnetic Additive Biomanufacturing Methods to Isolate, Sort Circulating Tumor Cells, and Microemboli/ Research Presentation, College of Engineering & Computer Science, Florida Atlantic University (invited talk)

2016: Micro- and Nano-scale Technologies for Applications Medicine/ Research Presentation, AES Electrophoresis Society's Annual Meeting, San Francisco, CA (plenary talk)

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International
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2016: Microscale Technologies for Bioengineering Applications in Medicine/Research Presentation, Dr. John W. McGregor Memorial Lecture, University of Alberta, Canada (Invited Keynote Speaker)

2016: Assembly and Joining Needs in Bio-N/MEMS/ Research Presentation, International Conference on Nanojoining and Microjoining, Niagara Falls, Ontario, Canada, 2016 (Invited Keynote Speaker)

Website(s) or other Internet site(s)
Nothing to report.

Technologies or techniques
Nothing to report.

Inventions, patent applications, and/or licenses
Nothing to report.

Other Products
Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Stanford University Personnel:

Name: Utkan Demirci
Project Role: PI
Research Identifier: utkandemirci (NIH agency login)
Month worked: 1 month
Contribution to Project: Supervision of project at Stanford.

Nearest person: Thomas Nieland
Project Role: Research Scientist
Research Identifier: none
Month worked: 2 months
Contribution to Project: Neuron isolation, create the cell assembling structure, embed cells in hydrogel for 3D culture and immunostaining

Nearest person: Jungkyu Choi
Project Role: Postdoctoral Research Fellow
Research Identifier: none
Month worked: 4 months
Contribution to Project: Isolation of cortical neurons, primary neuron cultures both in 2D and 3D, analysis of cultures via immunostaining

Nearest person: Murat Baday
Project Role: Postdoctoral Research Fellow
Research Identifier: none
Month worked: 3 months

Contribution to Project: Materials engineering, biomaterial modification, scaffold/hydrogel engineering, microscopy and and immunostaining.

University of Missouri Personnel:

Name: Zezong Gu
Project Role: co-PI
Research Identifier: zegunih1 (NIH agency login)
Month worked: 90 hours (0.6 months)
Contribution to Project: Supervision of project for the Missouri team. Visited blast site and wrote the University of Missouri animal protocols and research paper

Nearest person: Jiankun Cui
Project Role: Research Assistant Professor and Senior Personnel
Research Identifier: none
Month worked: 127 hours (0.8 months)
Contribution to Project: Visited blast site, assisted Dr. Gu for designing and planning experiments and writing the U of Missouri animal protocols. Prepared brain tissues for EM study, involved in research paper writing and editing

Name: Zhe Qu
Project Role: Specialty
Research Identifier: none
Month worked: 2.5 months
Contribution to Project: Dr. Zhe Qu in Gu lab visited the blast site multiple times, involving animal testing, training students, and taking care mice.

Name: Shanyan Chen
Project Role: Specialty
Research Identifier: none
Month worked: 2.9 months
Contribution to Project: Taking over Zhe's duties, involving animal testing, training students, immunostaining and taking care mice.

Name: Hailong Song
Project Role: Graduate Student
Research Identifier: none
Month worked: 3.2 months
Contribution to Project: Involving animal testing, and taking care mice, immunostaining, preparation of brain tissue and sections for EM, working with MU EM core facility for images, Analyzing EM images. He wrote the first draft of research paper.

Name: 2 other students in Gu lab
Project Role: students
Research Identifier: none
Month worked: 1.5 months
Contribution to Project: Involving animal testing and taking care mice, brain dissection. And analyzing EM images.

Name:	Graham Hubler
Project Role:	Consultant
Research Identifier:	none
Month worked:	55 hours
Contribution to Project:	Visited blast site, participated data analyzing and project discussion, involving research paper writing

Person:	Catherine E Johnson and her team
Project Role:	Engineer
Research Identifier:	none
Month worked:	74 hours
Contribution to Project:	Tested the blast settings and animal holding racks and platform, set up the container for animal housing and experimental preparation before open field blast, installed ventilation unit with temperature control and electricity to the animal unit on the blast site with 12 hours timed lights. The team has been analyzing physical data from blast sitting, involving research paper writing

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

PI, Utkan Demirci's other support has since charged in the closing of two grants and the addition of two grants.

What other organizations were involved as partners?

- **Organization Name:** University of Missouri
- **Location of Organization:** Columbia, MO
- **Partner's contribution to the projec**t
  - **Collaboration**: The University of Missouri is a subcontract on this grant. Their personnel and contributions are listed above.

8. **SPECIAL REPORTING REQUIREMENTS**

a. **COLLABORATIVE AWARDS:**
Nothing to report.

b. **QUAD CHARTS:**
Nothing to report.

9. **APPENDICES:**
   a. Publication

Behavioural Brain Research xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Linking blast physics to biological outcomes in mild traumatic brain injury: Narrative review and preliminary report of an open-field blast model

Hailong Song[a,b], Jiankun Cui[a,b,f], Agnes Simonyi[b,c], Catherine E. Johnson[d], Graham K. Hubler[e], Ralph G. DePalma[g], Zezong Gu[a,b,f,*]

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[b] Center for Translational Neuroscience, University of Missouri School of Medicine, Columbia, MO 65212, USA
[c] Biochemistry, University of Missouri School of Medicine, Columbia, MO 65212, USA
[d] Department of Mining and Nuclear Engineering, Missouri University of Science and Technology, Rolla, MO 65409, USA
[e] Sidney Kimmel Institute for Nuclear Renaissance, Department of Physics and Astronomy, University of Missouri, Columbia, MO 65211, USA
[f] Truman VA Hospital Research Service, Columbia, MO 65201, USA
[g] Office of Research and Development, Department of Veterans Affairs, Washington, DC 20420, USA

HIGHLIGHTS

- Blast exposures are associated with traumatic brain injury (TBI); during recent conflicts most of these have been classified as mild TBI (mTBI).
- The role and mechanisms of primary blast wave injury remain controversial. We review blast models of TBI including shock tubes and open-field blast.
- Our analyses of behavioral and pathological findings show that low level blast exposures (peak pressure < 100 kPa) induced lower mortality rates, fewer motor disabilities, and absence of lung injuries as compared to high level blast (peak pressure > 200 kPa).
- We present preliminary findings obtained from a reproducible open-field blast murine model of mTBI representing a primary low level blast injury. Within scalability limits, this model closely mimics low level battlefield blast exposures and offers opportunities to advance the understanding of blast physics, resulting neuropathology, and underlying mechanisms leading to chronic effects of mTBI.

ARTICLE INFO

Article history:
Received 22 July 2016
Received in revised form 13 August 2016
Accepted 19 August 2016
Available online xxx

Keywords:
Blast-induced TBI
Blast wave physics
Behavior
Neuropathology

ABSTRACT

Blast exposures are associated with traumatic brain injury (TBI) and blast-induced TBIs are common injuries affecting military personnel. Department of Defense and Veterans Administration (DoD/VA) reports for TBI indicated that the vast majority (82.3%) has been mild TBI (mTBI)/concussion. mTBI and associated posttraumatic stress disorders (PTSD) have been called "the invisible injury" of the current conflicts in Iraq and Afghanistan. These injuries induce varying degrees of neuropathological alterations and, in some cases, chronic cognitive, behavioral and neurological disorders. Appropriate animal models of blast-induced TBI will not only assist the understanding of physical characteristics of the blast, but also help to address the potential mechanisms. This report provides a brief overview of physical principles of blast, injury mechanisms related to blast exposure, current blast animal models, and the neurological behavioral and neuropathological findings related to blast injury in experimental settings. We describe relationships between blast peak pressures and the observed injuries. We also report preliminary use of a highly reproducible and intensity-graded blast murine model carried out in open-field with explosives, and describe physical and pathological findings in this experimental model. Our results indicate close relationships between blast intensities and neuropathology and behavioral deficits, particularly at low level blast intensities relevant to mTBI.

1. Introduction

Blast exposure is associated with traumatic brain injury (TBI), and also recognized as a potential risk factor for subsequent cognitive, behavioral disorders and possible chronic neurodegenerative disease [1–5]. During World War I, Frederick Mott first

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http://dx.doi.org/10.1016/j.bbr.2016.08.037
0166-4328/

reported findings in post-mortem brains of three blast exposed soldiers with no physical evidence of external head trauma; petechial hemorrhages, mostly within the white matter of corpus callosum, and internal capsule, were noted [6,7]. Later reports contributed to the understanding of the effects of penetrating brain injury in warfare by studying those injured in World War II and among Vietnam Veterans [8–10]. During the current conflicts in Iraq and Afghanistan [Operation Iraqi Freedom (OIF), Operation Enduring Freedom (OEF), and Operation New Dawn (OND)], the focus on severe and penetrating brain injuries has shifted to more commonly observed closed brain injuries, particularly those referred as mild TBI (mTBI) [11]. Since 2000, Department of Defense (DoD)'s report indicated that the vast majority (82.3%) of TBI has been classified as mTBI/concussion; while only approximately 1% comprising severe injuries [12]. Additionally, screening of one million combat veterans by the Veterans Health Administration (VHA) showed that approximately 8.4% of OEF/OIF/OND Veterans reporting and screened have received a diagnosis of TBI, most characterized as mTBI and, in great proportion, related to blast exposures [13,14]. 2016 recent Quarter 1 data again showed that mTBI constituted 86% of the total numbers of TBI [12]. Introduction of new and improved protective body armor in 2003 led to a marked reduction of traditional combat injuries [15,16]. Deaths from pulmonary damage were greatly reduced by enhanced protection of the torso; however, soldiers surviving combat related blasts appeared to be at higher risk of chronic effects of mTBI caused by explosive weaponry including exposures to widely used improvised explosive devices (IEDs) [17–20]. More importantly, the pattern of neuropathology caused by blast exposure observed in the military personnel may hold unique features not observed in those who have suffered blunt TBI [20–22].

The Glasgow Coma Score (GCS) is used to evaluate TBI severity [23]. For mTBI, the GCS ranges 13–15 and is characterized by: a confused or disoriented state lasting less than 24 h; loss of consciousness less than 30 min; memory loss lasting less than 24 h, and excludes penetrating TBI [12,24,25]. In experimental models, mTBI has been found to be associated with a variety of ultrastructural, biochemical, molecular, cellular, brain circuit and behavioral abnormalities [26,27]. This type of blast induced injury, mostly from IEDs, has been described clinically as an invisible injury, except when accompanied by tympanic membrane rupture [1]. About 15% of mTBI cases chronically associate with headaches, comorbid posttraumatic stress disorders (PTSD), depression, memory disturbances, or other cognitive dysfunctions [22,28]. It is often difficult to differentiate between the effects of blast TBI and PTSD, which may be the results of psychological stress/trauma [29–31]. Reconciling clinical reports of TBI exposure to blast in combat [17,18], and data from experimental TBI blast models [32,33] offers the prospects of better insights into the chronic symptoms of blast mTBI. This reconciliation may provide information about blast biomechanics and elucidate specific relationships between blast injury and later cognitive, behavior and neurological dysfunction.

We review underlying physical mechanisms of contemporary explosive devices and the spectrum of injuries inflicted by blast exposure, current shock tube and open-field mTBI animal models, and their associated behavioral and neuropathological outcomes. This narrative review is based on searches of the PubMed database using each of the terms "shock tube", "blast" or "open field blast" in combination with the terms "traumatic brain injury" or "brain trauma". Additionally, we describe a highly reproducible and intensity-graded open-field blast-induced murine model of mTBI, its subsequent macroscopic pathology findings, and how this model of open-field blast correlates with blast battle field exposure.

2. Physical principles of blast injuries

2.1. Types of blast injuries

Most combat blast-induced mTBIs are caused by explosive weaponry such as IEDs, rocket propelled grenades, and mortars [34]. Explosive blasts can result in primary, secondary, tertiary and quaternary injuries. Primary blast injuries occur as the blast wave impacts bodily structures. Most of the shock wave impact relates to the expanding overpressure zone [35]. The primary blast wave generates internal stress and strain forces in tissues and organs to cause injury. Furthermore, depending on position in relation to blast direction and surrounding structures, subjects are also exposed to complex blast waves caused by multiple reflections from the walls, ground, and their interactions [36]. Helmets have been shown to protect the brain from lateral and posterior blast exposure [37]. Additionally, body armor protects military personnel from most ballistic projectiles to the torso, reduces lung injuries and thus increases survival [38] and, as mentioned, the likelihood of living to experience the effects of TBI.

Secondary blast injury occurs when fragments from the explosive device or ground debris impact and penetrate into the body, and is characterized as the effect of projectiles. IEDs have metal casings and are usually filled with metal fragments. Tertiary blast injury, mainly due to the blast wind, occurs when the body is thrown through space into a structure such as a building, wall or the ground. Quaternary blast injury is due to burns, asphyxia, radiation, exposure to toxic inhalants [39,40]. Ultimately, primary injury due to blast exposure, similar to blunt trauma and ballistic penetration, relates to energy transfer from the external environment through the skull and its apertures and into the brain [41]. However, in primary blast wave injury, the modes of injuring mechanisms and coupling to tissues and structures are not immediately apparent.

2.2. Physics of explosive blast and underlying mechanisms of the blast injuries

Here, we consider the physical properties of the blast wave, translational and rotational head acceleration mechanisms, and a novel phonon-based physical model as causes of mTBI. As mentioned, potential mechanisms for blast-induced mTBI in the military environment include direct blast wave impingement, penetrating impact, blunt impact, among others [42].

2.2.1. Blast wave

Modern explosives produce pressure waves along with acoustic, electromagnetic, light and thermal energies [39]. Understanding blast wave dynamics, how they interact with the human body and how the body responds is a critical step towards understanding the blast-induced mTBI.

The triggering event in an explosion is detonation. The fundamental physics of blast detonation is rapid chemical decomposition of an explosive into the shock front and blast wind [43,44]. When an explosion occurs, space formerly occupied by the explosive material is virtually instantaneously filled with gas under high pressure and temperature. The resulting energy expands radially outward as a blast wave moving at supersonic speed. Thereafter, the explosion may also generate nonlinear and complex blast waves depending on location of the explosive material and nearby structures [1]. The Friedlander equation [45,46] characterized by a peak overpressure, duration, and impulse (integration of overpressure with respect to time) describes propagation of an ideal blast wave through time and space. A Friedlander plot depicts a very fast rise-time in positive pressure followed by an exponential decay to below atmospheric pressure (depending in some degree on the magnitude of the positive pressure rise) and ends upon return to atmospheric pressure

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[47,48]. The elapsed time where the blast pressure is greater than the ambient pressure (overpressure) is known as the positive-phase or impulse duration [49]. As the blast wave expands, peak shock overpressure decreases as a function of distance while its positive-phase duration increases. In high explosive blast waves, air is highly compressed on its leading edge (overpressure) creating a shock front [50]. As the shock wave expands, the density, pressure, temperature and velocity of air molecules decrease and the shocked air layer gives rise to rapidly moving air behind it, referred to as blast wind [51]. The high-pressure wave then radiates over a larger area, prolonging the duration of the over-pressurization phase. IEDs, in present conflicts, have been reported to cause a greater proportion of primary blast injuries than do conventional devices [52].

Explosive blast waves reflect off surrounding structures, including walls, buildings, vehicles and the ground. The resulting reflected pressures can be increased between two and eight times the incident pressure [51]. Reflection occurs when a single blast wave impinges on a surface, much the way an acoustic wave reflects off canyon walls creating echo. An exposed victim thus can be hit repeatedly from several directions by multiple blast waves emanating from a single explosion. Head and facial structures are more likely to be affected by direct blast wave transmission [53]. Additionally, a vascular surge from the thoracic or abdominal cavities may also transmit pressure waves into the brain [27,54]. Overall, blast injuries are caused by anatomical and physiological changes as a result of direct and reflective blast wave forces as these impact the body's surface and are transmitted internally.

2.2.2. Translational and rotational head acceleration

Holbourn's experimental observations using gelatin molds of brain sections showed that rotational acceleration induced widely distributed shear and tensile strains [55]. This effect may occur with long duration positive pressure phase blast waves to cause contusions and tissue shearing. A blast wave travelling at supersonic speeds can exert acceleration effects as it encounters the skull and the brain tissue [51,54]. At maximum peak pressures, simulations show that the head might be accelerated with forces up to 300G [56]. Inertial forces thus cause rapid brain motion within the skull as related to the cerebrospinal fluid (CSF) filled space between the skull and the brain to cause the brain compression and shear wave injuries [57]. Application of excess external forces also can cause the skull to collide with the brain or the brain to collide with the skull [58]. Additionally, these high impact forces may produce rotational effects causing brain injury due to stress forces, particularly at the interface between grey and white matter or between the cerebral hemispheres and the brain stem [41,55,59,60]. By contrast, blast exposure at intermediate distances may not produce notable impact or accelerating effects, while higher impacts cause brain deformation [61]. Relative motion between the brain and the skull caused by head rotational-translational acceleration can result in subdural hematomas through tearing of bridging veins. Intracerebral hematomas may occur due to parenchymal blood vessel rupture during brain and skull collision [62,63].

2.2.3. A novel phonon-based physical model for potential cause of mTBI

Experiments have demonstrated that mTBI can also occur as a result of non-impact and low-level primary blast [1,64]. The effects of such low-level impacts upon brain microstructure remain unclear. The local strain and stress of the brain tissue caused by low shock wave intensities appears insufficient to cause direct tissue damage. Such damage that does occur remains invisible to conventional brain imaging [65,66]. The fact that mTBI fails to provide grossly observable pathological effects may be explained by a unique physical mechanistic explanation related to the length scale of the shock wave transmitted into the skull to affect brain tissue. In 2012, Kucherov et al. [67] proposed a novel phonon-based biomechanical model for a potential cause of mTBI. The phonon is a quantum of energy or a quasiparticle associated with a compressional wave such as sound or a vibration of a crystal lattice. This model predicted that dimensions of brain tissue damage would occur within extremely small interval scales based upon water content of the brain and CSF: an injury range of ~200 nm that takes place within microseconds after the blast shock wave passes through brain tissue. This hypothesis assumes that brain tissue's physical properties, on the whole, are quantitatively similar to the properties of water [68]. CSF is even closer to water in its physical characteristics. Physical considerations predict that injury can occur 1000 times more rapidly than the milliseconds (ms) characterizing classic impact and acceleration injuries. The shock wave travelling through the brain excites a phonon continuum which decays into specific acoustic waves with intensity exceeding brain tissue strength. When the intensity of the resulting acoustic oscillations exceeds the tensile strength of water, water ruptures within microseconds of the passage of the shock wave through the brain during the phonon wave propagation. With blast exposures, the brain may be particularly susceptible to this type of phonon-mediated injury as compared to other tissues such as muscle. The resulting damage, measured in tens to hundreds of nanometers, occurs within the period of the phonon wave propagation and therefore is difficult to detect using conventional imaging modalities. This physical analysis correlates with predictions of low intensity blast pressures well known to induce mTBI in murine experimental models [27,69]. This phonon-based model has also been shown to accurately describe failure waves in brittle solids [70–72]. This proposed damage mechanism requires experimental verification using ultrastructural observations to detect damage measured in the range of 4–5 nm which may occur at intervals of several hundred nm.

3. Animal models and biological effects of blast related mTBI on behavior and neuropathology

3.1. Animal models of blast related mTBI

Experimental animal models have been used to address the fundamental questions related to blast-induced mTBI. Experimental approaches to examine the impact of blast waves on the brain and the consequences to mTBI require observations in live animals. Crucial questions related to blast-induced mTBI, such as physical properties and injury mechanisms can be delineated by use of reproducible experimental models. However, universal agreement between the behavioral and pathological findings observed in different animal models to military mTBI has yet to be achieved. This may due in part to the difficulty of producing primary shock waves, which maintain the characteristics of those caused by battle field blast exposures. Importantly, close proximity blast injuries are caused by high intensity blast waves due to the kinetic energy of the explosive process [73]. A large number of experimental settings have been used to simulate the blast injuries to study mTBI. The common forms include shock tube testing (denotation and compressed gas driven) and open-field blast settings [27,74–77]. Kobeissy et al. provides a list of recent experimental reports on primary blast injury [78]. Among these, only 8 of total 49 reports used explosive testing to model primary blast injury. The remaining 36 studies used shock tubes configurations and amongst those, 33 used compressed gas driven tubes. Collection of repeatable blast overpressure time data, including waveform, peak overpressure, duration, impulse, pressure transducer orientation, and post-shock wind, has been stressed as vital to produce highly consistent blast injuries for reproducible research results [79]. Accurate and repro-

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ducible data are also critical in translating and scaling animal findings into human injuries [32,80]. It remains essential to consider the potential for exposure scaling in the design of animal injury models; experimental scenarios should represent real-world exposures in so far as possible. We will later describe preliminary use of measured open-field blasts in a well characterized murine model.

3.1.1. Shock tube settings

Shock tubes are used in laboratory environments to produce a wide variety of repeatable blast waveforms which aim to model open-field blast waves [81]. Furthermore, shock tube testing is more economical and safe as compared to open-field blast settings [82]. However, the inherent disadvantages for shock tube experiments include the difficulties in generating shock waves approximating those due to battle field blasts, including reproduction of the reflected pressure from the "ground bounce", thermal and other blast effects. Shock tube configurations tend to yield complex shock waves following the original shock front. These include reflected shock waves, a Mach stem, an unsteady turbulent jet, and rarefaction waves in addition to animal positioning and shock tube blockage issues [83,84]. Complex waves within tubes can cause sudden compression or rarefaction effects upon objects in their motion path, thus transferring unusual high kinetic energy effects to animals within their path.

Shock tubes can be separated into the compressed gas driven and the denotation blast driven configurations. A compressed gas-driven shock tube consisting of horizontally mounted long circular steel tube used to simulate a dynamic shock wave was reported initially in 1955 [85]. These devices use a diaphragm, such as polyester Mylar membrane, to separate the device into two sections: a driven gas section at low pressure and a driver gas section at high pressure [86]. Shock tube diameter is determined by specimen size, with larger diameter to avoid confinement and blocking issues. Depending on the specimen dimensions, the tube diameter should be such that less than 5% blockage of the shock wave occurs [87]. After sudden rupture or removal of the diaphragm at pre-determined pressure thresholds, the pressure differential between the driver and driven gas generates shock waves which are propagated down the low pressure section (driven) towards the test object [88].

Two different driven section shock tube configurations are used to model biological blast effects. Close-ended shock tubes are capped at the end of the driven section. This design produces a stronger and more complex reflected shock wave back into the shock tube when the shock front reaches the end of the driven section [88]. Although, use of a close-ended configuration ensures that the incident shock wave presents as one-dimensional plane wave, the inability to dissipate the gases at the end of the shock tube also induces multiple reflections that propagate through the length of the tube. Therefore, the test object is affected by repeated complex shock waveforms as compared to the original shock front [84]. In contrast, open-ended shock tubes are not capped; this configuration is open to ambient air. The result is formation of a nearly spherical shock wave when the shock wave front reaches the open end of the tube and an expansion wave which propagates back into the shock tube [86]. For open-ended tube configurations, two different types use either inside or outside animal placement. Inside tube placement ensures the blast wave is a planar blast wave, but causes issues related to high pressure gas confinement leading to excessive applied impulse. To avoid excessive applied impulse, the inside tube diameter must be large enough, or the specimen must be placed quite close to the end of the tube. For the outside tube configurations, the test object must be placed close to the end of the shock tube to reduce expansion wave effects which complicate planar blast wave exposure [74].

Cernak and colleagues first described the ultrastructural and functional characteristics of blast injury in rats using a large-scale (39-m long with 1-m inner diameter, maximal overpressure 291 kPa with duration of 33 ms) shock tube to expose the whole body. A small-scale shock tube (0.5-m long with inner diameter of 10 mm, overpressure peak value 30–477 kPa) was used to expose localized pulmonary blast [89,90]. In 2011, Cernak et al. further developed a helium-compressed multi-chamber shock tube capable of reproducing complex shock wave signatures seen in theater and tailoring pressure wave signatures [33]. Along with this shock tube design, other variants were developed to mimic blast TBI, notably including the Walter Reed Army Institute of Research (WRAIR) shock tube setting [91]. Recently, advanced blast simulator with addition of an end wave eliminator and side-vented attenuator/diffuser attached to the shock tube have been developed to enable high fidelity and more accurate simulation of open-field blast waves [92,93]. Even with these ideal compressed gas driven shock tube settings, the resultant shockwaves can differ from the open-field blasts, particularly the duration and negative phases of the blasts. Simulation using a semi-analytical approach to predict the characteristics of pseudo blast waves that form in a compressed gas driven shock tube from test configuration parameters, along with other reports, indicate that if the shock tube parameters are not designed 'correctly', the resulting shock waves have a tendency to adopt trapezoidal shapes where the peak pressure plateaus before these decay as open-field blast waves do [77,94]. Identifying the initial location of blast wave formation is also important for proper placement of animal targets for experimental studies of blast-induced mTBI [95]. Existing shock tube experimental models have importantly identified pathological changes likely related to cardiovascular homeostatic mechanisms [74], as well as effects postulated to be due to electro-magnetic blast waves [27,96]; these efforts have been rewarding in advancing our knowledge of some aspects of blast injury. However, the shock tube models likely only partially imitate real life conditions and most of them have tested higher blast levels. Many rodent models exposed in compressed air-driven shock tubes sustain blast exposures with relatively low peak incident overpressures with large overpressure durations (greater than 10 ms). By contrast, real-world exposure of an IEDs composed of stacked artillery shells [97] produces overpressure durations typically much less than 10 ms [98].

For denotation blast shock tube configurations, the principles are the same as with compressed gas driven shock tube testing. The key difference between these two is that the blast shock tube uses a small explosive charge to generate high pressures rather than compressed gas [81,99,100]. The charge is detonated in a conical or parabolic driver section. Then the shock wave propagates down through the driven section as in compressed gas tubes [60,101,102]. A singular disadvantage of the blast shock tubes is that explosive use requires proper handling along with additional safety and security measures. These barriers appear to be the main reason that investigators favor compressed gas driven shock tubes as compared to blast tubes or the more direct paradigm using open-field explosive blast testing.

In summary, while valuable data has been obtained, the nature of the shock tube configurations and the generation of complex waves, conventional shock tubes may not model shock waves replicating those generated by free-field explosions. Reports describing shock tube apparatus and conditions, including but not limited to the design of the animal mounting rack and animal positioning (prone or supine), degree of head restraint, and relative location of the specimen to the tube, show considerable variation. These variations limit the extent of comparability and repeatability of experimental findings from different laboratories.

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3.1.2. Open-field blast settings

In 2011, two reports from investigators in Singapore and Israel described the use of open-field blasts to study TBI in rats and mice [75,76]. This approach appears intuitively more attractive for study of actual blast exposures. We describe progress using a highly repeatable open-field blast mTBI mouse model to elucidate the physical blast properties and its resulting pathophysiologic effects particularly for mTBI. The main advantage of open-field blast testing is that it closely replicates real-world blast scenarios in terms of similar overpressures and blast wave duration [98]. But, as previously mentioned, explosive use poses particular problems. This type of modeling is expensive and time consuming; it is difficult to find a safe and accessible open-field blast site; explosives (such as 2,4,6-trinitrotoluene, TNT; or composition C-4) must be handled carefully and stored in a safe and secure environment, and finally, uncontrolled environmental conditions (such as wind and temperature) may influence the blast setting and animal responses.

The Singapore report by Pun et al. demonstrated effects of a single sub-lethal blast over pressure exposure of either 7.1 PSI (48.9 kPa) or 11.3 PSI (77.3 kPa) upon rats in an open-field setting [76]. The animals were secured in metal cages that were anchored to the ground at the blast site and placed at either 24 or 30 m away from a TNT explosive source. A 0.4 by 0.4 m concrete block was interposed between the animals and the explosive source at a distance of 1.5 m from the animals to a shield against debris and protect animals against secondary blast injuries. These exposures resulted in petechiae and ecchymoses of lung tissues at day 4 and day 7 after blast. Darkened and shrunken neurons with the presence of perisomal spaces and narrowed vasculature at day 1 post blast as compared to control were found. However, this open-field setting presents serious drawbacks related to experimental blast design. First, the use of 120 kg of TNT resulted in mortality rates of 4.4% and 8.3% to model low and high blast, respectively. Deaths in the blast groups revealed pulmonary hemorrhage post-mortem. Secondly, the block used to protect against secondary blast injuries may have interfered with the shock front and also have generated reflected waves or other exposure variations [77].

Rubovitch et al. modeled an open-field mouse blast of mTBI using 500 g of TNT [75]. Anesthetized mice were placed in individual compartments on a platform 1 m above the ground at distances of 4 m and 7 m and covered with a plastic mesh, which let the animals rest in their natural position facing toward the blast wave source. Their heads were unshielded. Side-on pencil gauge sensors were used to monitor the blast peak overpressure. The mice at a distance of 7 m were exposed to 2.5 PSI (17.2 kPa) peak overpressure; at a distance of 4 m they were exposed to 5.5 PSI (37.9 kPa) peak overpressure. Fewer than 3% of the animals died as a consequence of these exposures and no gross pathological visual damage was recorded in internal organs 1 h and 24 h after blast. No alterations in basic neurological assessment or brain gross pathology were found acutely in the blast-exposed mice. However, cognitive deficits in novel object recognition (NOR) and Y maze tasks as well as axonal injuries persisted up to 30 days post blast. This open-field blast setting also had potential limitations regarding the animal holding compartment design. The animal holding compartment used in this study may block the primary blast wave transmission from the side and beneath. More importantly, the holding wall configuration might generate reflected pressure waves within each compartment, thus enhancing injury due to exposure to complex wave forms. The animals were placed on a holder, which may block additional reflected pressure from the "ground bounce" characteristic of open field blast injury [27,103]. Following this original report, three research articles using this model have been published. One used matrix-assisted laser desorption/ionization (MALDI) mass spectrometry imaging to track the distribution of gangliosides in mouse brain tissue [104]. They observed major increases of the ganglioside GM2 in the hippocampus (dentate gyrus and CA3), thalamus (thalamic parafascicular/centromedian nuclei and the lateral thalamus), and hypothalamus after 2 and 24 h (but not after 72 h) of a single blast exposure of 2.5 and 5.5 PSI. The second report compared the weight-drop physical impact model to the open-field blast setting, and identified unique gene expression using bioinformatics array analysis [105]. This study showed that TBI in mice induced by either physical or blast injury, led to the development of marked deficits in NOR compared to sham control 7 days after TBI, however with no difference in Y maze performance. Gene expression regulation and molecular pathways connected to Alzheimer's disease displayed a markedly different form of regulation depending on the type of TBI by their observations. The third article reported that blast induced cognitive deficits were potentially attenuated by pre- or post-injury treatment with the glucagon-like peptide-1 receptor agonist, exendin-4 (Ex-4) [106]. Ex-4, administered pre- or post-injury, ameliorated blast–induced neurodegeneration as measured by the ratio of Fluoro Jade B (FJB)/neuronal nuclear antigen (NeuN) positive cells at 72 h, memory deficits from days 7–14 (by NOR), and attenuated genes (*Stmn1* most up-regulated and *Megf9* most down-regulated) regulated by blast at day 14 post-injury.

Our group has recently established a highly reproducible open-field low-level blast intensity setting further refining the Rubovitch et al. open field model [75]. We used C-4 in a spherical configuration as the source of explosive placed 1 m above the ground. To ensure reproducible overpressures, we used four independent methods: (1) the blast simulator CONWEP software was used to set the conditions for Calculated Peak Pressure; (2) pressure gauges (137B23B – Quartz, free-field, ICP® blast pressure pencil probe, PCB Piezotronics, Depew, NY) were placed near the mice to measure pressure traces at a minimum sampling rate of 1 MHz or greater; (3) our animals were placed on a metal mesh fully accessible to the open-field shock waves from all directions; (4) test blasts with all equipment in place except for the mice were conducted and checked for accuracy and reproducibility. Our preliminary data using 350 g C-4 showed that 3 m distance group's measured peak pressure was 6.32 ± 0.16 PSI (~44.1 kPa) with overall positive phase duration of 2.97 ± 0.09 ms (data collected from 3 repetitive exposures). Both static and dynamic blast pressures including peak pressure vs. time and pressure vs. impulse curve data were also collected (Fig. 1A and B). Interestingly, we not only identified the shock wave approximating those occurring in the battlefield, but also observed an additional reflected pressure from the "ground bounce" following the original shock front as shown in Fig. 1A.

Combined with WRAIR shock tube data, our review and current experience with our open-field model suggests existence of a threshold between 74.5 and 116.7 kPa that separates low level blast from moderate to high level blast exposures. These exposures appear to be equivalent pathologically to human exposures ranging from moderate to severe TBI[107]. Studies from other laboratories using exposures of 74.5 kPa or lower also appear to be consistent with the WRAIR findings. Exposures in rats up to 74.5 kPa across a range of durations might reasonably be called low-level or mTBI blast exposure, causing only subtle or minor gross pathology, without lung trauma or death [64,76,108–110]. Our present model fits into the low level blast paradigm, consistent with peak overpressure data from prior reported studies [75,76]. No animal death or pulmonary trauma has occurred in the 3 m blast group (Fig. 2). Compared to other open-field explosive paradigms, the low level blast of our current explosive configurations offers a more appropriate experimental setting to model primary blast mTBI and, as described, will be pursued in further detail. Future plans include the study of blast exposed *in vitro* biofidelic 3-dimensional hydrogel micropatterns consisting of neurons and astrocytes. The use of this biofidelic brain model may further delineate intracellular nanoscale

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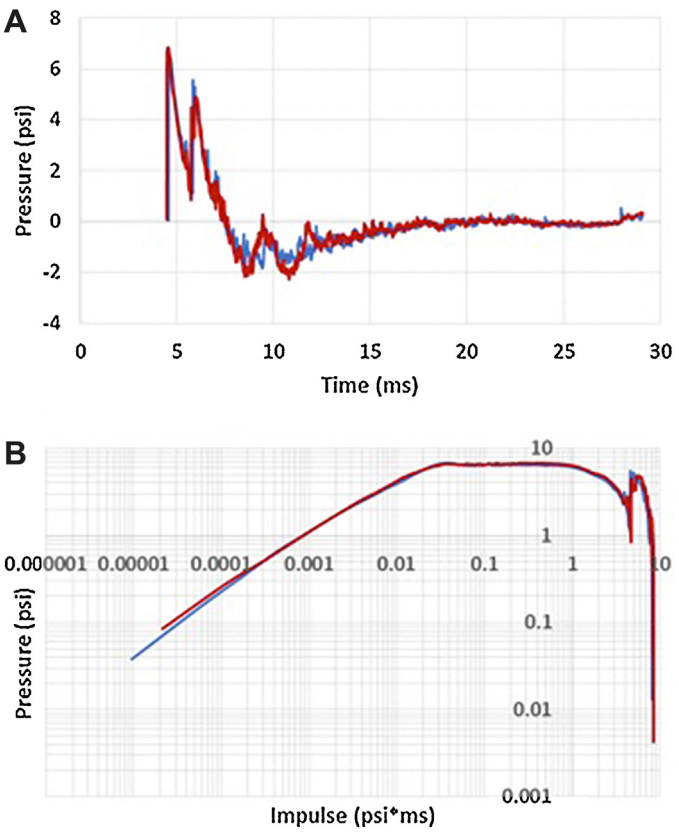

Fig. 1. Representative traces of the open-field blast peak pressure vs. time and pressure vs. impulse curve data.
(A) Blast with 350 g of C4 charge at standoff distances 3 m. Peak pressure vs. time for two parallel transducers (red and blue color) placed at 3 m platform. (B) Log-Log Pressure vs. Impulse curves for the two transducers at distance of 3 m.

effects in open-field blast injury [111]. This novel in vitro model provides an environment that respects the composition, geometry and functionality of brain circuits with fidelity unmatched by conventional *in vitro* 2D cultures.

3.2. Behavioral changes and neuropathology of blast related mTBI

We have searched and summarized original research articles focused on both shock tube and open-field blast setting using the PubMed database. Search terms included each of the terms "shock tube", "blast" or "open field blast" in combination with the terms "traumatic brain injury" or "brain trauma". No time limit was set with regard to publication date. Only English language articles were retrieved. Relevant articles related to blast TBI animal studies were selected on the basis of abstract review. Full articles were subsequently obtained and their references were searched for further relevant material. A total of 70 articles were selected and categorized into "low level blast impact (overpressure < 100 kPa)", "intermediate level blast impact (overpressure > 100 kPa and <200 kPa)", and "high level blast impact (overpressure > 200 kPa)" (detailed references were listed in Table 1). Forty-six of these studies used rats (male Wistar, Long Evans Hooded, or Sprague-Dawley) and the majority of the others used mice. Compressed gas driven shock tube (helium, nitrogen, or other) was most often used to model blast exposures. Analysis of these publications revealed that the mortality rates for animals are significantly and positively correlated with the blast overpressure ($r = 0.6546$, $P < 0.001$) (Fig. 3A). The mortality rate in both the low level and the intermediate level blast group was significantly lower than that occurring in the high level blast group (Fig. 3B).

Based on the summary of the behavioral outcomes (Table 1), we identified that low, intermediate, and high blast levels induced various degrees of behavioral dysfunction in terms of motor, learning, memory, cognition, emotion, and anxiety. Interestingly, the short term (within 7 days of the blast injury) outcome measures showed

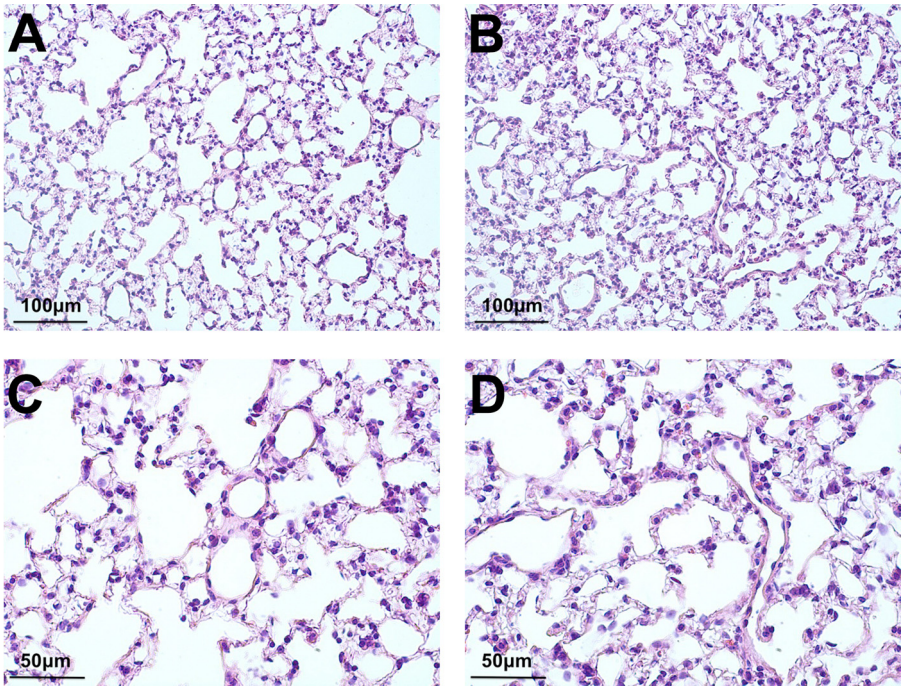

Fig. 2. Hematoxylin and eosin (H&E) staining for lung tissues in 3 m blast and sham group.
Histopathological specimens of lung tissues stained with H&E method. (A and C) 3 m blast group at 7 days under 20× and 40×. (B and D) Sham group at 7 days under 20× and 40×. Animal number, n = 3 for each group. No obvious difference was observed between the two groups.

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Table 1
Summary of research articles of the blast-induced behavioral outcomes.

Behavioral tests	Low level		Intermediate level		High level	
	Short-term	Long-term	Short-term	Long-term	Short-term	Long-term
Motor	2/6	1/3	3/5	2/2	1/1	1/1
Learning, memory, and cognition	5/7	5/5	3/4	5/5	5/6	3/4
Emotion and anxiety	2/4	2/2	3/5	4/5	3/4	2/4

Notes:
Low level: overpressure < 100 kPa, Refs.* [91,104,105,115,122–144];
Intermediate level: overpressure > 100 kPa and <200 kPa, Refs. [117,122,132,133,135,136,142,145–170];
High level: overpressure > 200 kPa, Refs.* [117,136,143,145,149,151,152,154,156,159,161,163,167,169–185].
*, References cited here are also for Table 2 and Table 3.
Short-term: tests done within 7 days of injury; Long-term: tests done after 14 days of injury.
#Numbers are based on papers with deficits in tasks/total papers assessing tasks.
#Motor: rotarod test, forelimb grip-strength test, staircase test, balance beam task, open-field, general neurological assessment.
#Learning, memory, and cognition: passive and active avoidance tasks, novel object recognition, Y maze, Morris water maze, Barnes maze, fear conditioning.
#Emotion and anxiety: acoustic startle response, open-field, elevated plus maze, light-dark box.

more impairments as compared to the long term (after 14 days of the blast injury) observations. Significant behavioral changes as well as neuropathology of mTBI can be induced by low level blast exposures in experimental animals [107,112]. In short term observations after a low level blast exposure, only 33% (2/6), 50% (2/4), and 71% (5/7) of the papers described motor dysfunction, emotional disturbances, as well as learning, memory and cognitive disabilities, respectively. While in long term observations, 100% (8/8 and 3/3) of the research articles identified learning, memory, and emotional behavioral changes characteristic of mTBI. Open field task was also used to examine anxiety and spontaneous exploratory (locomotor) activity. Blast exposed animals were found to exhibit anxiety-like or stress-related behaviors [106,113–115]. Findings from the Morris water maze documented impairments in spatial learning/memory defects [116–118]. Similar to those can be observed clinically in mTBI [107]. Other motor, cognitive, and emotional changes due to blast injuries have been assessed by using NOR, passive avoidance, elevated plus maze, light-dark box test, among others (see details in Table 1). Blast related animals also showed cognitive and emotional changes both in short-term and long-term [105,106,119]. Extrapolation of these results to human behaviors requires nuanced interpretation, but these behavioral findings in low level blast exposed animals are clearly important. These models provide important clues and insights into brain injury mechanisms causing mTBI.

Animal experiments also show that various degrees of eye, lung, and brain pathology occur in enhanced blast exposures. These

Table 2
Summary of the blast-induced macroscopic pathological outcomes.

Pathology findings	Low level	Intermediate level	High level
Lung	1/4	4/4	6/6
Eye	1/1	4/4	3/3
Brain	25/25	26/27	27/27

also can be modeled using open-field blast exposure. Based on literature review, we note that at low level (mild) blast overpressure (<100 kPa), less lung injury has been observed (1/4) as compared to intermediate (4/4) and high level blast (6/6). While rarely identified in human combat blast, animals subjected to a blast wave (130–290 kPa) (intermediate to high levels) showed moderate pulmonary hemorrhage, associated vascular damage, with direct alveolar injury, and edema. Another report using more than 183 kPa shock tube rupture pressure also showed that death occurred with extensive lung damage [33].

Blast exposure of animals also has induced tinnitus and central hearing impairment at a broad frequency range measured by gap detection and prepulse inhibition testing. These impairments tended to shift towards high frequencies over time [120]. Animal studies also confirmed greater degrees of pathological eye and brain outcomes (Table 2). Furthermore, our literature search indicated that cortical, hippocampal, and cerebellar tissue injuries were observed in all degrees of blast exposure along with hemorrhage/vascular injuries and white matter damage characterized as diffuse axonal injury (Table 3). The initial blast injury caused

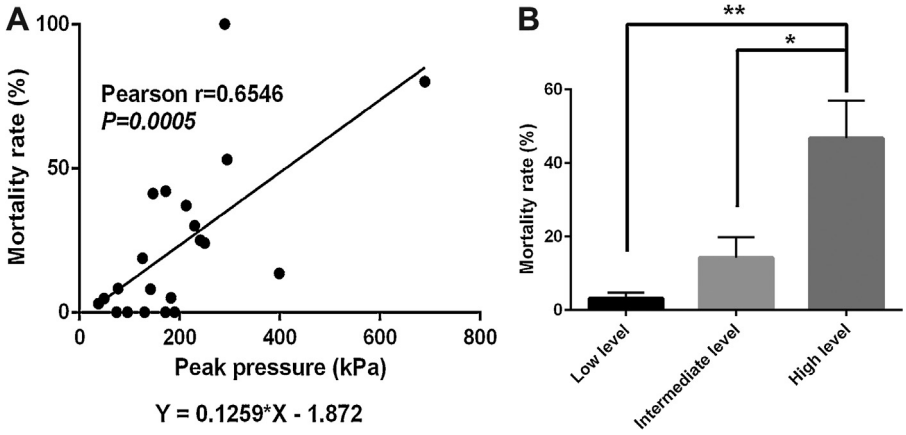

Fig. 3. Correlation of mortality rate of animals with blast peak pressure and comparison of mortality rate among different levels of blast peak pressure.
(A) The mortality rate (%) of experimental animals was significantly and positively correlated with the peak pressure (kPa) of the blast. The Pearson correlation r = 0.6546 and the $P = 0.0005$. The linear regression best-fit equation was "Mortality (%) = 0.1259 * peak overpressure – 1.872". (B) The comparison of the mortality rate among level, intermediate, and high level of blast pressure. The statistics was calculated using one-way ANOVA test. The P is 0.0025. (* $P < 0.05$; ** $P < 0.01$)

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Table 3
Summary of the blast-induced neuropathological outcomes.

Neuropathology findings	Low level	Intermediate level	High level
Cortex	8/8	7/7	4/4
Hippocampus	4/4	2/2	4/4
Cerebellum	2/2	3/3	2/2
Hemorrhage/Vascular injury	5/7	8/9	5/6
White matter damage	10/10	7/7	5/5

chronic changes in the microvasculature that were still evident many months after an 74.5 kPa blast exposure [121]. Additionally, in low level TBI animal exposures, axonal degeneration can be identified using silver staining [118]. Diffusion tensor imaging of mTBI mouse brain in the original Rubovitch model has shown axonal and myelin abnormalities that require further study [75]. Using our present low level open-field blast animals, we observed neither any death due to the blast, loss in vision, nor pulmonary injury (Fig. 2). The absence of more severe findings offers an important advantage for modeling mTBI since the blast overpressure of our maximum exposure is well below 74.5 kPa. Our open-field blast model relates to low level blast exposure was consistent with only subtle pathological changes in the absence of lung trauma and death [64,76,108–110]. In summary, we expect to identify behavioral changes and related pathological findings to characterize brain changes associated with mTBI.

4. Concluding remarks

The past decade of blast-induced TBI research yielded significant and novel findings concerning the physics of injury and its biological effects, particularly those that may cause mTBI. We have summarized underlying physical mechanisms of contemporary explosive devices and the spectrum of injuries inflicted by blasts/explosions, current shock tube and open-field mTBI animal models, and associated behavioral and neuropathological outcomes. Appropriate animal models of the blast-induced TBI will further deepen the understanding of physical mechanisms of the blast, and also assist in addressing the potential underlying mechanisms of the injury. On one hand, the majority of research articles on the blast-induced TBI used shock tube settings with various modifications; the data has provided useful information. However, open-field blast animal models have the unique ability to mimic actual blast explosions and multi-fold injuries occurring in modern combat exposures. We have described a highly reproducible blast murine model of mTBI using open-field exposure to C-4 explosives. The use of this open-field blast murine model may further establish relationships between the blast physical properties and mTBI/concussive injuries. Importantly, this model may also help to expand the available tools for researchers to study potential association between mTBI and later neurodegeneration.

Declaration of interest

Competing financial interests: none.

Acknowledgements

For Behavioural Brain Research Special Issue, this publication was made possible by funding from the Department of Pathology and Anatomical Sciences at the University of Missouri School of Medicine research fund (ZG), and DoD Congressionally Directed Medical Research Programs (CDMRP) and Peer Reviewed Alzheimer's Research Program (PRARP) Convergence Science Research Award AZ14009. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the United States government, the DoD, the United States Army or the Department of Veterans Affairs.

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Please cite this article in press as: H. Song, et al., Linking blast physics to biological outcomes in mild traumatic brain injury: Narrative review and preliminary report of an open-field blast model, Behav Brain Res (2016), http://dx.doi.org/10.1016/j.bbr.2016.08.037

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